Z Gastroenterol 2016; 54(12): 1343-1404
DOI: 10.1055/s-0036-1597375

**1. Fibrogenesis**

Georg Thieme Verlag KG Stuttgart · New York

**Thyroid Hormone Receptor (TR): a regulator in Liver Fibrogenesis**

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**Abstract**

Thyroid hormone (TH) signaling is critical for tissue-organ development, growth, differentiation and metabolism, and in the liver, the most widely expressed TH receptor is TRβ. In a recent study of patients with nonalcoholic steatohepatitis (NASH), progressive liver fibrosis was associated with disrupted TH signaling. In a separate study, low serum triiodothyronine (T3) was associated with advanced NASH-fibrosis. These findings suggest that TH signaling may be a novel regulator of adult liver fibrogenesis. Herein, we hypothesized that the TH-TR axis modulates HSC phenotype and perturbations in TH-TR axis occur during liver injury.

**Methods:** In vivo: Two murine liver injury models were used (6 weeks of methionine choline deficient (MCD) diet and 6 weeks carbon tetrachloride (CCL4) injection). Human tissues were obtained from explanted NASH and healthy donor livers. Liver fibrosis was assessed by Sirius Red (SR) staining, αSMA immunohistochemistry, and the hepatic hydroxyproline assay. Total liver expression of TRα and TRβ, αSMA and Collagen 1α1 mRNA were determined by qRT-PCR. In vitro: To determine whether TH modulates HSC activation, primary HSC and a HSC line were treated with transforming growth factor (TGF)-β (5 ng/ml), in the presence or absence of T3 (10 ng/ml). TRα knockdown in HSC was achieved using lentiviral-mediated shRNA (shTRα). Results were confirmed using TRα knock-out (TRαKO) mouse embryonic fibroblasts (MEF). HSC migration was assessed using the wound healing assay, western blot and qRT-PCR (αSMA, collagen 1α1, TRα and β). Hepatocytes were used as positive control for TRβ expression.

**Results:** Total liver TRα and TRβ mRNA were downregulated by 4-fold (p < 0.05) during liver fibrogenesis in mice and humans. In HSC, TRα is the predominant TR (4 fold higher than TRβ; p < 0.05). TGF-β stimulation of HSC repressed TRα and TRβ mRNA expression, but this effect was blunted by T3. shTRα-HSC exhibited greater activation at baseline, with increased fibrogenesis markers αSMA and collagen 1α1, and enhanced responses to TGF-β (increased p-Smad2/3). shTRα-HSC also had greater response in wound-healing assay (1.3-fold, p < 0.05), which was consistent with enriched contractility/migration pathways obtained from RNA sequencing analysis.

**Conclusions:** Liver expression of TRα and β is repressed during fibrogenesis following chronic liver injury. TRα is the predominant TR in HSC and perturbations in TH-TR levels regulate HSC phenotype via the TGF-β pathway. Future studies will be needed to determine if whether TH treatment could inhibit liver fibrosis progression.